Influenza

For many years, influenza vaccines have been considered "adult" vaccines. This will change with the new recommendation for vaccination of all children.

Influenza is a highly infectious acute viral illness. Epidemics of what was probably influenza have been reported since at least the 16th century. There were at least 3 global epidemics, known as pandemics, in the last hundred years. What is sometimes cited as the biggest and deadliest pandemic of all time, the 1918-1919 pandemic of so called Spanish influenza, killed an estimated 21 million persons of all ages worldwide.

Influenza is an orthomyxovirus which was first isolated in 1933. There are 3 types: A, B, C. Type A causes moderate to severe illness in all age groups. Type B generally causes milder epidemics and primarily affects children. Type C does not cause epidemics and is rarely reported in humans. Type A has subtypes which are determined by two surface antigens, hemagglutinin and neuraminidase. This is an illustration of the surface of the influenza virus. Hemagglutinin, the blue spikes, help the virus attach to cells. Neuraminidase, the green knobs, facilitate the release of mature virus from infected cells. Three types of hemagglutinin and 2 types of neuraminidase have been described for human influenza viruses. Type A influenza viruses are subtyped, or grouped, depending on the type of H and N they have. For instance, one of the current strains of influenza A virus has type 3 hemagglutinin and type 2 neuraminidase. This virus is identified as H3N2.

A person's immunity to the surface antigens, particularly hemagglutinin, reduces the likelihood of infection with influenza virus, and reduces the severity of disease if infection occurs. Antibody against one influenza virus type or subtype provides little or no protection against another type or subtype. Unfortunately, the structure of the surface antigens changes over time. These changes allow influenza virus to evade our immune response to prior influenza infection or vaccination. The result is that most of us will experience repeated infections with influenza viruses throughout out lifetime, and the components of the vaccine must be changed frequently.

There are two types of antigenic changes that the influenza virus undergoes – drift and shift. Antigenic drift is a relatively minor change within the same subtype. It results from point mutations in the gene coding for hemagglutinin, and occurs during viral replication. Antigenic drift may be associated with epidemics, depending on how different the new virus is from the prior one. Drift occurs continually, from year to year, or even within the same year. Antigenic shift is a major change which creates a new virus subtype. This new subtype usually replaces its predecessor. Antigenic shift is probably due to genetic recombination

between human and nonhuman influenza viruses. This type of change is associated with pandemics, because the entire population of the world is susceptible to this new virus. These major changes do not happen frequently, but when they do, a major pandemic may follow.

There have been 3 antigenic shifts in the last 100 years, which occurred about every 10 to 40 years. The last major shift was in 1968, 36 years ago. Influenza experts believe it is not a question of IF influenza virus will shift again. It is only a matter of **when** the shift will occur. There is concern that a new pandemic virus could emerge in Asia. Since mid-December 2003, 8 Asian countries have confirmed outbreaks of highly pathogenic avian influenza caused by the influenza A H5N1 strain. As of March 8, 2004, 32 human cases of H5N1 influenza, including 22 deaths, have been confirmed in Thailand and Vietnam.

In response to these outbreaks, the World Health Organization and the ministries of health of the affected countries have instituted very aggressive control measures, including the destruction of infected chickens and ducks, in an attempt to avert a new pandemic. During the past 2 months, more than 100 million birds in Asia have either died of the disease or been culled. It is not known if H5N1 is, or could be, the next pandemic virus. But even if it is not, a new pandemic virus will arise eventually, so we need to be ready for it.

Influenza viruses change continually, and sometimes change radically, which means we may experience influenza illness more than once, **and** the vaccine components may need to be changed annually. Fortunately, only a few strains of virus circulate at any given time. For the last 20 years, only 2 type A's and 1 type B have circulated concurrently.

The clinical features of influenza run the gamut from mild to severe, or even fatal. Infection with influenza virus can also lead to life-threatening complications. Transmission of influenza is by respiratory droplets. The incubation period is short – 1 to 5 days. There is usually an abrupt onset of fever, myalgia, sore throat, nonproductive cough, and headache. Severity of illness from influenza depends on prior immunologic experience with antigenically related variants. That means that if you are exposed to a drifted strain, similar to the one you had the year before, the illness will probably be mild. But if the virus has drifted a lot -- or worse, shifted – the illness may be severe, even if you had influenza the previous year.

Influenza is a respiratory disease, and the major complication is pneumonia. It can be either primary influenza pneumonia, or secondary bacterial pneumonia, commonly due to pneumococcus. Pneumococcal pneumonia is a common complication of influenza because the nasopharynx of many people are colonized with the organism. Pneumococcus just takes advantage of the damage done by the influenza virus. In addition, the nasopharynx of patients in a hospital or long term care setting may be colonized with other bacteria, such as *Staphlococcus aureus* or Pseudomonas. These organisms may be resistant to multiple antibiotics. If a person in a hospital or long term care facility develops

influenza, the pneumonia that follows may be due to one of these resistant bacteria. That is why it is so important to prevent influenza outbreaks in institutional settings. If the influenza is not fatal, the resulting pneumonia could be. Reye syndrome is an infrequent complication, and occurs in children taking aspirin. Myocarditis is inflammation of the heart, and is a relatively rare complication. Overall, death from influenza occurs once in every 1,000 to 2,000 cases, but is much more frequent in certain populations.

Influenza is the most frequent cause of death from a vaccine preventable disease in the United States. During 1990 through 1999, approximately 36,000 influenza-associated pulmonary and circulatory deaths occurred during each influenza season. Influenza seasons in which H3N2 viruses predominate are associated with higher mortality. Persons 65 years and older account for more than 90% of deaths attributed to pneumonia and influenza. Persons with underlying medical conditions account for most of the remaining 10% of deaths.

There was a lot of media attention of influenza-related deaths among children during the 2003-2004 influenza season. Influenza-associated death is not a reportable condition in the United States, so the true number of such deaths is not known. Mathematical models estimate approximately 92 influenza-associated deaths occur annually among children 5 years of age and younger. As of mid-February 2004, 135 influenza-associated deaths among children younger than 18 years of age have been reported to CDC from 38 states. About 60% of these deaths were among children 5 years of age and younger. 50% had one or more underlying medical condition. However, the majority of affected children were not in groups for which routine vaccination was recommended this year. Very few of the children who died had been vaccinated.

In addition to fatalities, influenza is also responsible for an average of 114,000 hospitalizations per year. Although persons 65 years and older are at the highest risk of dying from influenza, other age groups are at nearly as high risk for influenza-associated hospitalization. This table summarizes age-specific rates of influenza related hospitalizations per 100,000 population from several published studies. The rates among persons at high risk of complications are shown in the center column, and those not at high risk in the right column. Children birth to 4 years of age had rates of hospitalization higher than any other age group through age 64 years. The hospitalization rate among children younger than 4 years was 500 per 100,000 population, 5 times higher than healthy children of the same age. This rate of hospitalization was higher than any other age group with high risk conditions through age 64, and in some of the studies even higher than persons 65 years of age and older with high risk conditions. The risk of complications and hospitalization is not equal for all children. This table shows rates of influenza-related hospitalizations by age in a Medicaid population in Tennessee. By far the highest rates of hospitalization were among children 11 months of age and younger, particularly those with high risk conditions, shown in the center column. But rates of hospitalization are very high through 2 years of age in both healthy children and those with high risk conditions. Rates of hospitalization in children younger than 2 years are similar to those of persons 65 and older with high risk medical conditions. To reduce this burden of disease

among young children, ACIP and the American Academies of Pediatrics and Family Physicians will recommend routine influenza vaccination of all children 6 through 23 months of age, beginning in influenza season 2004. We will discuss this issue in more detail a little later.

In summary, influenza is a short incubation period disease caused by a virus that changes continuously. Influenza virus is responsible for thousands of deaths each year, even without a major antigenic change. Most complications and deaths from influenza occur in persons 65 and older, those with underlying illnesses, and young children.

Inactivated influenza vaccine has a longer history than most vaccines we use. The first effective influenza vaccines were produced in the mid-1930s. The discovery in the 1940s that influenza virus grew well in embryonated chicken eggs allowed large scale production of inactivated influenza vaccines. Influenza became the first genetically engineered vaccine in 1971, when this technique was used to improve virus yields needed for vaccine production.

There are two main types of influenza vaccines available in the U.S.: a live attenuated influenza vaccine, abbreviated LAIV, and an inactivated subunit vaccine, which we will abbreviate TIV. There are two subtypes of TIV. These two subtypes contain either split virus, or purified surface antigens. There is no longer a whole inactivated virus vaccine available in this country.

Live attenuated influenza vaccine was licensed by the Food and Drug Administration in June 2003. The vaccine is produced by MedImmune and marketed with the name FluMist. It is distributed by Wyeth Vaccines. LAIV has several unique properties in addition to being a live virus vaccine. The live influenza viruses in the vaccine are attenuated, and produce mild or no signs or symptoms related to influenza virus infection. They are temperature sensitive, which means they do not replicate efficiently at 38-39^{o} Celsius. This property prevents the live viruses from replicating efficiently in the lower airways. The viruses are also cold adapted, which means they replicate efficiently at the temperature of the upper airway, 25^{o} Celsius. This temperature is permissive for replication of LAIV viruses but restrictive for replication of many wild type viruses. What this means is that LAIV is able to replicate in the mucosa of the nasopharynx, which produces protective immunity against the viruses in the vaccine. On the other hand, the viruses are attenuated and do not replicate effectively in the lungs, so they cannot produce influenza disease. LAIV does not contain thimerosal or gelatin.

Because LAIV contains live attenuated influenza viruses, the vaccine viruses can be shed from the vaccinated person, and possibly be transmitted from vaccinees to other persons. Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. In a study in a daycare setting, 80% of vaccinated children 8-36 months of age shed at least one virus strain for an average of 7.6 days. In this study, one instance of transmission of vaccine virus to a contact was documented. The transmitted virus was identical to the

original vaccine virus. A small study of 20 healthy vaccinated adults 18-49 years of age demonstrated that most shedding in this age group occurred within the first 3 days after vaccination. No subject shed vaccine viruses 10 or more days after vaccination. Person-to-person transmission of vaccine viruses was not assessed in this study. Because of the potential for shedding and transmission of vaccine virus by healthy adolescents and adults, ACIP prefers that LAIV **not** be administered to persons in close contact with severely immunosuppressed persons.

All current influenza vaccines are trivalent, meaning that they contain 3 different viruses, H3N2, H1N1, and B. The viruses contained in the vaccines are chosen each spring, based on surveillance of current circulating strains. Vaccine efficacy varies. It depends on the recipient and the similarity of the vaccine virus to the circulating virus. The duration of immunity for inactivated influenza vaccine is considered to be 1 year or less. The duration of immunity for LAIV uncertain, but may be longer than for TIV.

Following inactivated influenza vaccine, antibody wanes in a few months, and may fall below protective levels. The virus may also drift, so the antibody to the VACCINE virus is less effective. This would apply to both LAIV and TIV. Antigenic drift was a problem with the 2003-2004 vaccine. The virus that circulated (A/Fujian) was a drift variant of the vaccine virus (A/Panama). The difference between the two viruses was enough that the vaccine did not provide much protection against the circulating virus.

The efficacy of inactivated influenza vaccine in preventing clinical illness also hinges on several **recipient** factors. Age and underlying illness are the main recipient factors. For example, if there is a good match between the inactivated vaccine and circulating influenza strains, the inactivated vaccine is 70% to 90% effective in preventing clinical illness among healthy persons younger than 65 years of age. The problem is that it is only 30% to 40% effective in preventing illness among older persons. The **real value** of TIV is that it prevents complications and death from influenza, even among frail elderly persons. Here is a graph that shows the percent of nursing home residents who were hospitalized, developed pneumonia, or died, following an influenza outbreak. The green bars represent residents vaccinated with inactivated influenza vaccine and the tan bars represent the unvaccinated residents. Unvaccinated residents were twice as likely to be hospitalized, more than twice as likely to develop pneumonia, and more than 4 times as likely to die as residents who were vaccinated with inactivated influenza vaccine. Studies have compared the ability of LAIV and TIV to protect adults against laboratory-confirmed influenza. Overall, LAIV was 85% effective and TIV was 71% effective. There was no statistically significant difference in vaccine efficacy between these two types of vaccines in this age group. The take away message for either type of influenza vaccine is that they do not prevent illness as well as we would like, but vaccinated persons have milder illness and significantly fewer complications as a result of the infection.

Two manufacturers are expected to supply inactivated influenza vaccine during the next influenza season. Aventis Pasteur produces a split virus vaccine that they call Fluzone. Chiron produces a vaccine that was formerly made by Evans called Fluvirin. The Chiron vaccine is unique because it contains purified surface antigens. The Chiron influenza vaccine is not approved for use in children 4 years of age and younger. This is because safety and efficacy in this age group has not been demonstrated in clinical trials. Providers who vaccinate children should use Aventis Pasteur split virus vaccine for children 6-47 months of age.

Here are the viruses selected for the 2004 - 2005 formulation. One of the strains is the same as last year's vaccine. This is the H1N1 strain called A/ New Caledonia/20/99. The H3N2 strain will be A/Fujian/411/2002, and the B strain will be B/Shanghai/361/2002. Do not worry if the vaccine you get next year does not list these viruses. The manufacturers may use antigenically identical virus strains with different names because their growth properties simplify the manufacturing process.

The schedule for inactivated influenza vaccine is relatively simple – one **intramuscular** dose per year. But the dose is not the same for all age groups, and some persons need 2 doses. Here is the routine schedule for inactivated influenza vaccine. The minimum age is 6 months. No influenza vaccine is approved for children younger than 6 months of age. Children 6 months through 35 months of age receive a 0.25 mL dose – half the dose of an older child or adult. Recipients 3 years of age and older should receive a 0.5 mL dose. Children 6 months through 8 years of age receiving TIV for the first time should receive **two** doses separated by four weeks. The first dose is an immunologic primer. Children 3 through 8 years who have previously received influenza vaccine need only one dose. Persons 9 years of age or older receive one annual dose because by this age our immune system has been primed the hard way – with wild-type influenza virus.

Live attenuated influenza vaccine is approved only for healthy persons 5 through 49 years of age. Do not administer LAIV to children younger than 5 years, or to persons older than 49 years. The dose of LAIV is 0.5 mL, divided equally between the nostrils. The dose is the same regardless of age. Children 5 through 8 years of age who have not previously received any type of influenza vaccine should receive 2 doses of LAIV, separated by 6 to 10 weeks. Notice that this is a longer interval than the 4 weeks separating two doses of inactivated influenza vaccine. Children 5 through 8 years of age who have previously received influenza vaccine should receive one dose of LAIV. One dose is recommended for persons 9 through 49 years of age, again because it's presumed they have already been primed through exposure to wild-type viruses. The LAIV manufacturer recommends that children 5 through 8 years of age who have never been previously vaccinated with LAIV should receive 2 doses of LAIV. However, ACIP recommends that if children in this age group have previously received inactivated influenza vaccine, they need only **one** dose of LAIV.

A child receiving influenza vaccine for the first time may not return for the second dose 4 weeks later. Next year, you can count the dose this year as the primer. The child needs only one dose next year, and in subsequent years. LAIV does not contain thimerosal, a mercury-containing preservative. However, most inactivated influenza vaccine distributed in the United States does contain thimerosal.

For the 2004-2005 influenza season, a limited number of doses of reduced thimerosal-content influenza vaccine will be available. The reduced thimerosal formulations will contain less than 1 microgram of thimerosal per dose, compared to 25 micrograms per dose for regular inactivated influenza vaccine. Reduced thimerosal formulations are available from both manufacturers of inactivated influenza vaccines. The inactivated Chiron vaccine is approved by FDA for persons 4 years of age and older. It should not be administered to children 6 months through 47 months of age. The inactivated Aventis Pasteur vaccine is available in two forms – a 0.25 mL single dose package for children 6 through 35 months of age, and a 0.5 mL single dose package for children 3 years of age and older. Aventis will also produce a preservative-free pediatric formulation for children 6 to 35 months of age.

We know that influenza virus can cause severe illness and death among children and other high-risk persons. ACIP believes that the benefit of inactivated influenza vaccine with reduced or standard thimerosal content outweighs the theoretical risk, if any, from thimerosal.

Lets talk about who should receive influenza vaccine. This issue has gotten a bit more complicated with the arrival of LAIV, since indications for it differ from those for inactivated influenza vaccine. We will discuss recommendations for TIV first. Our basic strategy for TIV is to target the groups most likely to experience severe influenza illness and complications, and persons in contact with these high-risk groups. The risk factors for severe illness and complications from influenza are age, chronic illness, pregnancy, and aspirin use in children. We will show you the specifics in the next few graphics.

The targeted groups for TIV include all persons 50 years of age or older, persons 6 months of age and older with certain chronic illnesses, and healthy children 6 through 23 months of age. In 2000, the age for routine vaccination with TIV was lowered from 65 to 50 years because coverage among middle-aged people with high-risk conditions was low. Up to a third of persons 50 through 64 years of age have a high-risk condition, but only about 40% of these people received influenza vaccine during the 2000 influenza season. Age-based vaccination strategies are generally more effective than strategies based on medical conditions. So targeting everyone 50 through 64 years of age will likely increase vaccination levels among people with high-risk conditions in this age group.

As we discussed earlier, influenza is a common cause of respiratory illness among children. Rates of hospitalization among children younger than 24 months of age are as high as rates among seniors. In 2003, ACIP, and the Academies of

Pediatrics and Family Physicians agreed that the time had come to recommend routine annual inactivated influenza vaccination of **all** children 6-23 months of age. This recommendation will begin with the 2004-2005 influenza season. Both the 2004 ACIP influenza statement and a new childhood and adolescent immunization schedule to be published in July 2004 will reflect this recommendation.

Persons with chronic illnesses should be considered for inactivated influenza vaccination. Chronic illnesses include pulmonary disease, such as emphysema and asthma; cardiovascular disease; and metabolic diseases like diabetes. They also include renal dysfunction, like chronic renal failure or nephropathy; hemoglobinopathy, like sickle cell disease, and immunosuppression, including HIV. In addition to people 50 and older and people with chronic illness, the target group for TIV includes residents of long term care facilities, persons 6 months through 18 years of age receiving chronic aspirin therapy because of their risk of Reye syndrome, and pregnant women.

Pregnant women are a group at increased risk for complications of influenza. Excess deaths from influenza among pregnant women were documented during the pandemics of 1918-1919, and 1957-1958. Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza. A study published in 1998 found that the risk of hospitalization for influenza-related complications was more than 4 times higher for women in the second or third trimester of pregnancy than for nonpregnant women. The risk of complications for these pregnant women was comparable to nonpregnant women with high-risk medical conditions. Beginning in the 2004-2005 influenza season, ACIP will recommend vaccination with inactivated influenza vaccine for all women who will be pregnant during the influenza season. This is a change from previous recommendations for vaccination of pregnant women who would be beyond 14 weeks of gestation during the influenza season. ACIP reviewed the available data at its February 2004 meeting and concluded that there is no evidence that inactivated influenza vaccination in the first trimester puts the pregnancy at risk. Pregnant women who also have other high-risk medical conditions, such as heart or lung disease, should also be vaccinated with TIV **before** the influenza season begins. LAIV is contraindicated for pregnant women and we will talk more about this later.

The majority of inactivated influenza vaccine distributed in the United States contains thimerosal as a preservative. A substantial margin of safety has been incorporated into the health guidance values for organic mercury exposure. TIV formulations with reduced thimerosal content are also available from both manufacturers. If you have reduced thimerosal vaccine available, it can be administered to pregnant women. If you do not have the reduced thimerosal formulation, you should not hesitate to administer standard influenza vaccine to pregnant women.

Here are the persons who, when immunized, help protect the highest risk groups from exposure to influenza: healthcare providers, including home care providers.

Next, employees of long term care facilities – and not just the nurses and doctors. Do not forget the nursing aides, housekeepers, physical therapists, dieticians, and anyone else who shares air with the patients. Finally, there are the household members of high-risk persons who, if immunized, could keep influenza out of the home. This includes all household members of children younger than 2 years of age, particularly infants. These household members are a group for whom LAIV could also be used.

Available data suggests that persons with HIV may have prolonged influenza illnesses, and are at higher risk of complications of influenza. Clinical trials of persons with HIV infection have demonstrated that even those with low CD4 T-cell counts respond well to inactivated influenza vaccine. Although a transient increase in HIV replication has been reported, there is no evidence of deterioration in the CD4 count, and no progression of clinical HIV disease. ACIP believes that inactivated influenza vaccination will benefit many HIV infected persons, including HIV-infected pregnant women. LAIV should not be administered to persons with HIV infection.

The primary objective of influenza vaccination is to protect those at highest risk of complications and death from influenza. The second objective is to prevent influenza in the persons who might transmit the virus to these high-risk groups. But influenza vaccine can be considered for other groups. Other groups to consider for vaccination include providers of essential community services. Foreign travelers and students living in dormitories. Finally, anyone who wants to reduce their likelihood of influenza should get vaccinated. If the persons in these groups are 5-49 years of age and healthy, they would be candidates for LAIV. Use of LAIV in healthy people could help conserve TIV for the groups who are not able to receive LAIV.

ACIP has been discussing routine influenza vaccination of 6 through 23 month old children for more than 2 years. In March 2003, in anticipation of this recommendation, the Vaccines for Children (VFC) program expanded eligibility for inactivated influenza vaccine coverage. This expanded coverage includes all VFC-eligible children 6 through 23 months of age, and 2-18 years of age with household contacts younger than 2 years. VFC-eligible children 6 months and older with high-risk medical conditions continue to be covered.

Another important component of our annual influenza vaccination program is its timing. As you are aware, there were substantial delays in the distribution of influenza vaccine in 2000 and 2001. Vaccine was in short supply in 2003 because of increased demand, not because of a production delay. Influenza vaccine production is complex, and it is possible that delays in distribution could occur again. To minimize disruptions caused by these delays, ACIP now recommends that providers focus their vaccination efforts in October and earlier on persons 50 years of age and older; persons younger than 50 years at high risk of complications of influenza, including children 6-23 months of age; and household contacts of high risk persons, including out-of-home caregivers and household contacts of children 23 months of age and younger. Also in October

you should vaccinate healthcare workers. Finally, vaccination of children 6 months to 9 years of age who are receiving vaccine for the first time should also begin in October because they need a second dose 1 month after the initial dose. Vaccination of all other groups should begin in November.

To avoid missed opportunities for vaccination, vaccine should be offered to persons at increased risk of complications of influenza when they access medical care beginning in September, if vaccine is available. Vaccination of high-risk persons early is easier if offices have a reminder and recall system in place.

We receive many questions about administration of a **second dose** of TIV in the same season, particularly among high-risk persons vaccinated in September or October. There are few data to support the need for a second dose in a season. ACIP does NOT recommend administration of more than one dose of influenza vaccine per season for any group, except children 6 months to 9 years of age receiving influenza vaccine for the first time.

Influenza season typically peaks in January and February in the United States. However, on rare occasions it has peaked as late as May. ACIP recommends that providers should continue to offer influenza vaccine to their patients, especially to those at high risk of complications, and to healthcare workers for as long as influenza viruses are circulating in their communities. This may mean vaccinating past November and December. ACIP believes that live attenuated influenza vaccine can be an important adjunct to the use of inactivated influenza vaccine. However, LAIV will not be a substitute for inactivated influenza vaccine, particularly among the groups at highest risk of complications of influenza.

LAIV is currently approved for use **only** for healthy persons 5-49 years of age. This group includes persons who wish to reduce their risk of influenza, and many persons in close contact with high-risk groups. These persons now have the option of choosing either TIV or LAIV. LAIV should not be used in young children, or persons 50 years of age and older. It also should not be used in anyone with an underlying medical condition that increases the person's risk of complications of influenza. TIV should be used for these groups.

Close contacts of persons at high risk for complications of influenza should receive influenza vaccine. This reduces the risk of transmission of wild-type influenza viruses to high-risk individuals. There are no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts. In the absence of such data, use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with severely immunosuppressed individuals. This means that healthcare workers may receive LAIV as long as they are not in contact with severely immunocompromised persons, such as a person with a recent bone marrow transplant. The preference for TIV in this situation is because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the immunosuppressed individual and cause disease. ACIP states no preference between TIV and LAIV for vaccination of healthy persons aged 5-49 years in close contact with all other high-risk groups.

The manufacturer's package insert recommends that LAIV not be administered concurrently with other vaccines. This is because it is not known whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, ACIP recommends that providers follow the simultaneous administration guidelines published in the General Recommendations on Immunization. Inactivated vaccines do not interfere with the immune response to live vaccines. Inactivated vaccines – such as tetanus and diphtheria toxoids – can be administered either simultaneously or at any time before or after LAIV. Other live vaccines can be administered at the same visit as LAIV. However, live vaccines not administered on the same day should be delayed at least 4 weeks, when possible.

There are no data on the effect of LAIV on a tuberculin skin test. Mucosally administered vaccines, such as OPV, are not believed to affect a PPD. So until other data becomes available, we do not recommend restrictions on tuberculin skin testing in LAIV recipients. PPD can be applied any time before or after LAIV administration.

The adverse reaction profile for the inactivated influenza vaccine is not much different from other inactivated vaccines. As you would expect from any inactivated vaccine, the most common adverse reactions are local reactions. From 15% to 20% of TIV recipients report local reactions, like pain at the injection site. Systemic events, like fever and malaise are not common. They occur most commonly in persons without prior exposure to the antigens in the vaccine, particularly young children. Severe allergic reactions are rare, and are most likely related to residual egg protein when they do occur. Good screening can essentially eliminate the risk of allergic reactions in influenza vaccine recipients. Neurological reactions, specifically Guillian Barré syndrome, are very rare. GBS has not been clearly associated with the inactivated influenza vaccine since the swine flu vaccine in 1976. TIV is inactivated, so it cannot cause influenza. However, it is possible to get influenza **after** vaccination. It takes a week or two to develop a good immune response to the vaccine. But since the incubation period is only a few days, you could get flu if you were exposed shortly after vaccination, before the vaccine has a chance to work.

In clinical trials among children 12-59 months of age, LAIV recipients had a significantly increased risk of asthma or reactive airways disease. LAIV has not been shown to cause increased rates of upper respiratory illness symptoms, fever, or other systemic symptoms among children. In some studies of adults, LAIV recipients experienced statistically significant increased rates of cough, coryza, nasal congestion, sore throat, and chills. No increase in the occurrence of fever has been identified among adults. No serious adverse reactions with LAIV have been identified in either children or adults.

Contraindications and precautions differ between inactivated and live attenuated inactivated influenza vaccines. Those to TIV are the same as most other

inactivated vaccines. A history of a severe allergic reaction to a vaccine component or following a prior dose of vaccine is the only contraindication. Needless to say, persons with a severe egg allergy should not receive influenza vaccine. Moderate or severe acute illness is a precaution, and vaccination should be deferred until the acute illness has improved. A history of Guillian Barré syndrome, or GBS, is not an automatic contraindication for inactivated influenza vaccination. The association between inactivated influenza vaccine and GBS is discussed in detail in the influenza ACIP statement. You should be familiar with it. The bottom line is that the benefit of TIV outweighs the risk of a second occurrence of GBS in persons at high risk of complications of influenza.

There is quite a long list of contraindications for LAIV. It might help to think of LAIV as being **contraindicated** for most persons for whom inactivated influenza vaccine is **indicated**. TIV should be considered in most persons for whom LAIV is contraindicated. LAIV is contraindicated for persons younger than 5 years or 50 years of age and older. Persons with underlying medical conditions should not receive LAIV. This includes persons with immunosuppression from any cause. Children 18 years and younger receiving chronic aspirin therapy should not receive LAIV because of the risk of Reye syndrome. Pregnant women should not receive LAIV, but should be routinely vaccinated with TIV. According to the manufacturer, persons with a history of Guillain Barré Syndrome should not receive LAIV. As with all vaccines, a severe allergic reaction to a vaccine component or following a prior dose is a contraindication for LAIV. The viruses in LAIV are grown in chicken eggs, so severe egg allergy would be a concern, like it is for TIV. Likewise, vaccination with LAIV should be deferred in persons with a moderate or severe acute illness. LAIV can be administered to persons with minor acute illnesses. However, if you believe that nasal congestion is present in such a degree as to impede delivery of the vaccine, defer administration until the illness resolves.

The vaccine viruses in LAIV are extremely fragile, so storage and handling of this vaccine is critical. The viruses in LAIV have no tolerance for heat. LAIV must be stored at or below minus 15^{o} Celsius, which is 5^{o} Fahrenheit, at all times. The vaccine cannot tolerate storage temperature warmer than -15^{o}. So LAIV cannot be stored in a frost-free freezer. This is because the temperature in a frost-free freezer may rise above -15^{o} Celsius during the defrost cycle. LAIV must be stored **only** in a manual defrost freezer that can reliably maintain -15^{o} Celsius. If you do not have access to a manual defrost freezer, then you must store LAIV in a special manufacturer-supplied freezer box. In general, you will keep the vaccine frozen until immediately before it is used, at which time you will thaw it in your hand. LAIV may also be thawed in a refrigerator. However, it can be stored at refrigerator temperatures – which are $2\text{-}8^{o}$ Celsius – for no more than 24 hours prior to use. Any LAIV that is kept at refrigerator temperatures for more than 24 hours must be discarded.

The sprayer is not just a modified syringe. It is a specially designed device with a one-way aerosol dispersion tip that produces a fine mist. The plastic clip on the plunger divides the dose in half. One half of each dose is sprayed, or misted, into

each nostril. The mist is not uncomfortable for the person being vaccinated. If the person should sneeze or cough during or after administration, the dose does **not** need to be repeated.

At its February 2004 meeting, ACIP discussed the issue of administration of LAIV. It is likely that transient environmental contamination with vaccine virus is unavoidable. The risk of infection of the person administering the vaccine is unknown, but probably small. ACIP recommends that severely immunosuppressed persons should not administer LAIV. Practically, this means that a person who is immunocompetent enough to come to work is also immunocompetent enough to administer LAIV.

We do not have time during this program to discuss antiviral drugs for the prevention or treatment of influenza virus infection. However, there is an extensive discussion of this topic in the influenza ACIP statement. The 2004 statement is expected to be published in MMWR around the end of April.

As we mentioned earlier, there is little doubt that the influenza virus will shift again, and that there will be another influenza pandemic in the future. The problem is that we do not know when it will happen. Although we cannot predict when the next pandemic will occur, we can try to prepare for it. In July 2000, we produced a satellite broadcast that described the impact of pandemic influenza, and how to plan for it. The program was called Preparing for the Next Influenza Pandemic. It was intended to help public health officials with the process of assessing their needs, and organizing a response to pandemic influenza. A videotape of this broadcast is available free of charge from the National Immunization Program at www.cdc.gov/nip.